FUNCTIONAL ANTAGONISM OF NEUROPEPTIDE Y RECEPTORS, A. J. Daniels, Department of Pharmacology, Glaxo Wellcome Inc., Research Triangle Park, NC 27709.

The molecular determinants that govern neuropeptide Y binding to its receptors has been the subject of numerous studies. Research in this area has focused primarily on understanding which regions of NPY are essential for optimal affinity, biological activity, and receptor-subtype selectivity. There seems to be consensus that N- and C-terminal amino acids of NPY are essential for strong receptor interaction. Towards our ultimate goal of designing nonpeptide antagonists of NPY, we attempted to determine first the minimum structural requirements for receptor binding and activity. Our strategy focused on the examination of a series of C-terminal amidated short peptides containing aromatic and positively charged amino acids. A systematic structure-activity/activity study, led us to conclude that incorporation of the discontinuous epitope Try^{1}, Arg^{35} and Tyr^{36}-NH_2 into appropriately substituted pentapeptides, was sufficient to allow interaction with low micromolar affinity towards rat brain NPY receptors. Extension of these pentapeptides at the N-terminus, with the amino acids contained in NPY^{27-31}, generated an NPY agonist (YINLIYRLRY-NH_2) half as potent at NPY in inducing intracellular calcium increase in HEL cells and, in increasing mean arterial blood pressure in rats. Surprisingly, replacement of Leu^{4} by Pro in the above peptide agonist, afforded an NPY antagonist (YINPIYRLRY-NH_2) with nanomolar affinity for NPY receptors. Subsequent dimerization, via disulfide or lactam bridges, of a series of deca- and nonapeptides related to the above antagonist, afforded ligands with picomolar affinity for rat brain NPY receptors and potent antagonism for Y1 receptors in in Vitro and in in Vivo assays. It is of interest to note that while these dimers show an apparent high affinity for rat brain receptors (Y2 type mainly) they do not seem to interact with Y2 receptors in peripheral tissues such as the rat vas deferens. The latter suggests that central and peripheral Y2 receptors may represent different sub types of NPY receptors. The compounds described here represent a first generation of high affinity NPY receptor antagonists, which will help unveil the role of endogenous NPY in important physiological functions. In addition, these compounds may assist in the development of novel therapeutic agents to treat central as well as peripheral pathologies associated with an NPYergic transmission hyperactivity.

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